

# Synthesis and Structure–Activity Relationships for the Fungicidal Activity of *O,O*-bisaryl *sec*-butylphosphonates

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**Abstract:** Sixteen *O,O*-bisaryl *sec*-butylphosphonates have been synthesised by condensing *sec*-butylphosphonyl dichloride with substituted phenols. The compounds were tested against two phytopathogenic fungi, *Rhizoctonia bataticola* and *Helminthosporium oryzae*. The most active compound against *R. bataticola* is *O,O*-bis(3-methylphenyl) *sec*-butylphosphonate ( $ED_{50}$  29.56 mg litre<sup>-1</sup>) and against *H. oryzae*, *O,O*-bis(2-chlorophenyl) *sec*-butylphosphonate and its *para*-chloro analogue ( $ED_{50}$  0.14 and 0.13 mg litre<sup>-1</sup> respectively). Quantitative structure–activity relationships on the fungicidal activity have been analysed by means of multiple regression analysis using physicochemical substituent parameters. Electronic parameters viz.,  $\sigma$  and  $F$  have expressed significant variability in fungitoxicity against both the fungi, viz. *R. bataticola* and *H. oryzae*. Hydrophobic and steric parameters are also found to be important in the correlation studies.

**Key words:** synthesis, fungicidal activity, quantitative structure–activity relationships, *Rhizoctonia bataticola*, *Helminthosporium oryzae*, *O,O*-bisaryl *sec*-butylphosphonates

## 1 INTRODUCTION

Organophosphonates reveal good fungicidal activity.<sup>1</sup> A few recent reports from this laboratory have shown that branched chain alkyl groups in organophosphonates increase fungicidal activity. The present investigation is an extension of earlier work wherein the fungicidal activity of bisaryl isopropylphosphonates has been reported.<sup>2</sup> The effect of lengthening the branched-chain alkyl group by one carbon atom on the fungicidal activity is the theme of this present study. Accordingly, a series of *O,O*-bisaryl *sec*-butylphosphonates have been synthesised and evaluated for their fungicidal activity against *Helminthosporium oryzae* B. de Haan and *Rhizoctonia bataticola* (Taub) Britton-Jones, destructive pathogens to cereals and vegetable crops. The quantitative structure–activity relationships of the new phosphonates are also described in this article.

## 2 EXPERIMENTAL METHODS

### 2.1 Synthesis of *O,O*-bisaryl *sec*-butylphosphonates

The sequence of reaction leading to the synthesis of *O,O*-bisaryl *sec*-butylphosphonates (**III**) is depicted in Fig. 1.

#### 2.1.1 Synthesis of *sec*-butyl chloride (**I**)

*sec*-Butyl chloride was prepared as described in literature<sup>3</sup> by reacting *sec*-butyl alcohol with concentrated hydrochloric acid in the presence of anhydrous zinc chloride; b.p. 68–70°C, yielding 69.3%.

#### 2.1.2 Synthesis of *sec*-butylphosphonic dichloride (**II**)

*sec*-Butylphosphonic dichloride was prepared as described in the literature<sup>4</sup> by reacting *sec*-butyl chloride with aluminium chloride and phosphorus trichloride followed by hydrolysis with water; b.p. 59°C/3 mm Hg, yielding 83%.

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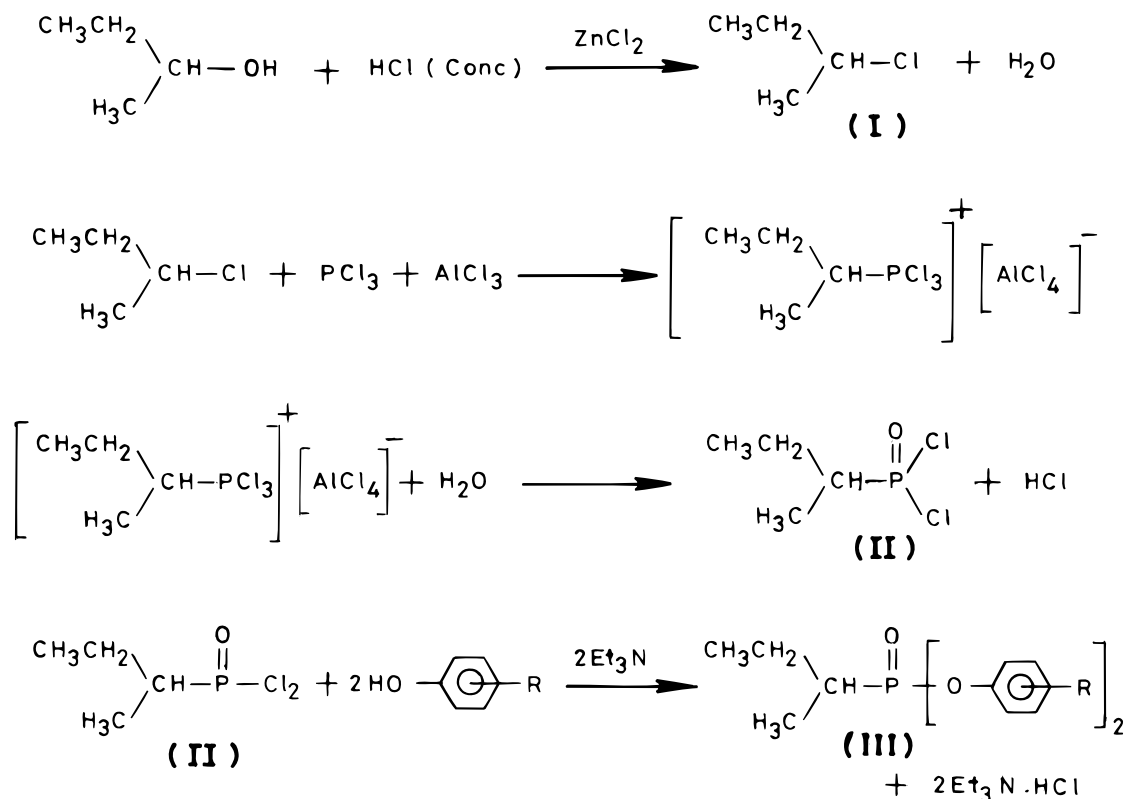


Fig. 1. Schematic presentation of the synthesis of *O,O*-bisaryl *sec*-butylphosphonates.

### 2.1.3 Synthesis of *O,O*-bisaryl *sec*-butylphosphonates (III)

A solution of *sec*-butylphosphonic dichloride (II, 1 mole) in dry benzene was added dropwise to a solution of the appropriate phenol (2 moles) in dry benzene containing dry triethylamine (2 moles) with constant stirring at 65–70°C. The stirring was continued for 8–10 h. The precipitate of triethylamine hydrochloride was filtered off and the solvent removed by distillation. The residual viscous liquid product was then purified by washing with sodium hydroxide solution (20 g litre<sup>-1</sup>) to remove untreated phenol, followed by washing with water to remove traces of alkali. Further purification was achieved by column chromatography over silica gel for liquid products, while solid products were recrystallised from a mixture of light-petroleum distillate + benzene (4 + 1 by volume), (Table 1). The purity of the phosphonates was checked by TLC over silica gel using benzene + acetone (4 + 1 by volume) as developing solvent and iodine vapour as visualising agent.

## 2.2 Structure identification by spectroscopy

### 2.2.1 IR spectroscopy

IR spectra were recorded in a Nicolet Fourier Transform Infra-red Spectrometer (Model Impact 400) as thin film for liquid samples and as potassium bromide pellets for solid samples ( $\nu$  max. in cm<sup>-1</sup>). IR spectra showed characteristic peaks for P=O, P-O & O-C stretching

vibrations of P-O-C (aromatic) and their values were in accordance with the proposed structures.

### 2.2.2 NMR spectroscopy

[<sup>1</sup>H]NMR spectra were recorded on a Varian EM-360L, 60 MHz instrument in carbon tetrachloride/deuteriochloroform using tetramethylsilane as internal standard (chemical shifts expressed in  $\delta$  ppm). The characteristic feature of [<sup>1</sup>H]NMR spectra of III was the presence of  $\beta'$ -proton coupling by phosphorus nucleus where the signal split into a double doublet due to vicinal coupling with the  $\alpha$ -proton and with the phosphorus nucleus. The high field half of this double doublet merged with the triplet signal of  $\gamma$ -protons which made it difficult to assign J-values for the double doublet of  $\beta'$ -proton signal as well as for the triplet of  $\gamma$ -proton signal. The signal of  $\alpha$ -proton and  $\beta$ -proton merged together to give rise to a multiplet, thus increasing the complexity of the spectra.

## 2.3 Fungitoxicity study

The synthesised *O,O*-bisaryl *sec*-butylphosphonates were screened for their fungicidal activity against *R. bataticola* and *H. oryzae* by the poisoned food technique using potato dextrose agar (PDA) medium.<sup>5</sup> The corrected percentage inhibition data were fed to a BASIC LD<sub>50</sub> programme version 1.1<sup>6</sup> to get ED<sub>50</sub> (effective dose in mg litre<sup>-1</sup> required for 50% inhibition of fungal growth) values of the compounds (Table 2).

**TABLE 1**  
Physical and Analytical Data of O,O-bisaryl sec-butylphosphonates

Compd No.	<i>R</i> <sup>a</sup>	<i>m.p.</i> <sup>b</sup> (°C)	Yield (%)	Elemental analysis			
				Found (%)		Calc. (%)	
				C	H	C	H
1	H	L	84.5	66.15	6.50	66.21	6.55
2	2-CH <sub>3</sub>	L	85.9	67.70	7.20	67.97	7.23
3	3-CH <sub>3</sub>	L	85.4	67.81	6.28	67.92	7.23
4	4-CH <sub>3</sub>	L	86.9	67.60	7.22	67.92	7.23
5	2-Cl	L	82.8	53.10	4.69	53.48	4.74
6	4-Cl	L	70.3	53.50	4.76	53.48	4.74
7	4-Br	L	82.5	42.80	3.27	42.86	3.79
8	2-OCH <sub>3</sub>	67.5	74.2	61.50	6.52	61.71	6.57
9	4-OCH <sub>3</sub>	L	82.5	61.40	6.55	61.71	6.57
10	4-SCH <sub>3</sub>	L	86.8	56.02	6.00	56.54	6.02
11	2-NO <sub>2</sub>	L	65.4	50.20	4.40	50.52	4.47
12	4-NO <sub>2</sub>	65.0	14.6	50.50	4.31	50.52	4.47
13	4-C(CH <sub>3</sub> ) <sub>3</sub>	64.0	87.5	71.55	8.80	71.64	8.71
14	2,4-Cl <sub>2</sub>	L	80.2	44.77	3.54	44.86	3.50
15	2,4,5-Cl <sub>3</sub>	68.0	75.8	38.50	2.60	38.63	2.61
16	2,4,6-Cl <sub>3</sub>	118.5	65.5	38.60	2.59	38.63	2.61

<sup>a</sup> See Fig. 1, III.

<sup>b</sup> L: Liquid compounds purified by column chromatography.

## 2.4 Quantitative structure–activity relationship (QSAR) studies

QSAR studies were carried out on the fungicidal activity of 16 O,O-bisaryl sec-butylphosphonates for the two test fungi. The physicochemical parameters of the

phenyl ring substituents were correlated with the fungitoxicity values of the compounds using multiple regression analysis with a computer programme S.P.S.S. The significance of the regression equation was judged from the values of multiple correlation coefficient (*R*), square of multiple correlation coefficient (*R*<sup>2</sup>), the standard

**TABLE 2**  
Fungicidal Activity of O,O-bisaryl sec-butylphosphonates

Compd No.	<i>R</i> <sup>a</sup>	<i>ED</i> <sub>50</sub> (mg litre <sup>-1</sup> )	
		Rhizoctonia bataticola	Helminthosporium oryzae
1	H	63.38	9.07
2	2-CH <sub>3</sub>	34.22	8.46
3	3-CH <sub>3</sub>	29.56	6.17
4	4-CH <sub>3</sub>	47.53	24.86
5	2-Cl	259.8	0.14
6	4-Cl	713.62	0.13
7	4-Br	756.99	0.63
8	2-OCH <sub>3</sub>	101.86	114.15
9	4-OCH <sub>3</sub>	50.96	12.98
10	4-SCH <sub>3</sub>	> 1000	15.78
11	2-NO <sub>2</sub>	81.96	68.50
12	4-NO <sub>2</sub>	> 1000	> 1000
13	4-C(CH <sub>3</sub> ) <sub>3</sub>	> 1000	> 1000
14	2,4-Cl <sub>2</sub>	> 1000	16.93
15	2,4,5-Cl <sub>3</sub>	> 1000	33.32
16	2,4,6-Cl <sub>3</sub>	> 1000	39.86
	Edifenphos <sup>b</sup>	43.0	10.0

<sup>a</sup> See Fig. 1, III.

<sup>b</sup> Reference standard used in fungicidal assay.

error (s), value of  $F$  test ( $F$ ) and the level at which the value of  $F$  was significant ( $\text{Prob} > F$ ).

The  $\text{pED}_{50}(\text{M})$  value for the fungicidal activity was considered as dependent variable where the  $\text{ED}_{50}$  value expressed in  $\text{mg litre}^{-1}$  was converted into  $\text{mole litre}^{-1}$  [ $\text{ED}_{50}(\text{M})$ ]. The physicochemical parameters of the phenyl ring substituents taken as independent variables were (Table 3): (i) hydrophobicity parameter,  $\pi$  (Hansch constant)<sup>7</sup> (ii) electronic parameters (a)  $\sigma_p$  and  $\sigma_m$  (Hammett constant)<sup>7</sup> (b) Swain-Lupton constant ( $F$ ) for 'proximity polar effect'<sup>8</sup> (for *ortho*-substituent) and (iii) steric parameters<sup>7</sup> (a) Taft-steric parameters ( $E_s$ ) for *ortho*-, *meta*- and *para*-substituents. (b) Verloop STERIMOL parameters ( $L$ ,  $B_1$  and  $B_4$ ) for *ortho*-, *meta*- and *para*-substituents.

### 3 RESULTS AND DISCUSSION

#### 3.1 Fungicidal activity

Fungicidal activity was evaluated in terms of  $\text{ED}_{50}$  values expressed in  $\text{mg litre}^{-1}$  (Table 2). The compounds which could not show 50% growth inhibition at  $1000 \text{ mg litre}^{-1}$  have been reported as  $\text{ED}_{50} > 1000$ .

Compound Nos **2** to **13** contained only one substituent in the phenyl ring. In the case of *R. bataticola*, the methyl-substituted compounds showed maximum activity in comparison to other substituted compounds of the series. The 3-methylphenyl compound (**3**) was the most active in the whole series ( $\text{ED}_{50} 29.56 \text{ mg litre}^{-1}$ )

against this fungus. In the case of *H. oryzae* also, compound **3** ( $\text{ED}_{50} 6.17 \text{ mg litre}^{-1}$ ) was found to be more active than the 2-methyl (**2**) and 4-methyl (**4**) compounds. Against *R. bataticola* and *H. oryzae*, the order of fungicidal activity was  $3\text{-CH}_3 > 2\text{-CH}_3 > 4\text{-CH}_3$ . *R. bataticola* was found to be much more tolerant to the mono-halogen substituted compounds (**5**, **6** and **7**). Maximum activity was shown by the 4-chlorophenyl compound (**6**,  $\text{ED}_{50} 0.13 \text{ mg litre}^{-1}$ ) in case of *H. oryzae*. The activity against *H. oryzae* was in the order  $4\text{-Cl} > 2\text{-Cl} > 4\text{-Br}$ . The methoxy compounds showed moderate activity against both the test fungi. The 4-methoxy compound (**9**) was found more active than the 2-methoxy analogue (**8**) in both cases ( $\text{ED}_{50} 50.96 \text{ mg litre}^{-1}$  against *R. bataticola* and  $\text{ED}_{50} 12.98 \text{ mg litre}^{-1}$  against *H. oryzae*). The 4-thiomethyl compound (**10**) exhibited good activity only against *H. oryzae* ( $\text{ED}_{50} 15.78 \text{ mg litre}^{-1}$ ). The 2-nitrophenyl compound (**11**) showed moderate activity against both the test fungi, but the 4-nitro analogue (**12**) and 4-*tert*-butyl derivative (**13**) were inactive against both the test fungi.

The 2,4-dichlorophenyl compound (**14**) was found to be inactive against *R. bataticola* whereas it showed very good activity against *H. oryzae* ( $\text{ED}_{50} 16.93 \text{ mg litre}^{-1}$ ).

Neither of the trichloro compounds, viz. 2,4,5-trichloro (**15**) and 2,4,6-trichloro (**16**) showed any activity against *R. bataticola* but they possessed good activity against *H. oryzae* ( $\text{ED}_{50} 33.32$  and  $39.86 \text{ mg litre}^{-1}$  respectively).

Against *R. bataticola* the 2- and 3-methyl phenyl compounds (**2** and **3**,  $\text{ED}_{50} 34.22$  and  $29.56 \text{ mg litre}^{-1}$

TABLE 3  
Substituent Parameter Constants used for the QSAR Studies

Substituents in <b>III</b> <sup>a</sup>	$\pi$	$\sigma^b$	$F$	$L$	$B_1$ <sup>c</sup>	$B_4$	$E_s^d$
H	0.0	0.0	0.0	2.06	1.0	1.0	0.0
CH <sub>3</sub>	0.56	−0.17 (−0.07)	−0.04	3.00	1.52	2.04	−1.24
Cl	0.71	0.23 (0.37)	0.41	3.52	1.80	1.80	−0.97
Br	0.86	0.23 (0.39)	0.44	3.83	1.95	1.95	−1.16
NO <sub>2</sub>	−0.28	0.78 (0.71)	0.67	3.44	1.70	2.44	−2.52
OCH <sub>3</sub>	−0.02	−0.27 (0.12)	0.26	3.98	1.35	2.87	−0.55
SCH <sub>3</sub>	0.61	0.00 (0.15)	0.20	4.30	1.70	3.26	−1.07
C(CH <sub>3</sub> ) <sub>3</sub>	1.98	−0.20 (−0.10)	−0.07	4.11	2.59	2.97	−2.75

<sup>a</sup> See Fig. 1.

<sup>b</sup>  $\sigma$  values given in parentheses are for *meta*-substituents while others are for *ortho* and *para*-substituents.

<sup>c</sup> Used in case of *H. oryzae*.

<sup>d</sup> Used in case of *R. bataticola*.

respectively) showed better activity than the reference fungicide edifenphos ( $ED_{50}$  43.00 mg litre<sup>-1</sup>). However, the 4-methylphenyl compound ( $ED_{50}$  47.53 mg litre<sup>-1</sup>) showed similar activity to edifenphos against *R. bataticola*. The 2- and 3-methylphenyl compounds (**2** and **3**;  $ED_{50}$  8.46 and 6.17 mg litre<sup>-1</sup> respectively) had superior activity to edifenphos (10.00 mg litre<sup>-1</sup>) against *H. oryzae*. The 2-chloro, 4-chloro and 4-bromophenyl compounds (**5**, **6** and **7**;  $ED_{50}$ , 0.14, 0.13 and 0.63 mg litre<sup>-1</sup> respectively) also exhibited much superior activity to edifenphos.

### 3.2 QSAR studies

It is observed from the multiple regression equations that, as one increases the numbers of variables in the equation the value of  $R^2$  increases but at a lower rate. Considering the practical feasibility for maximisation of the values of the physicochemical parameters to obtain the most active compound and considering  $R^2$  values, models up to four variables are listed here (eqns (1) to (8)).

#### 3.2.1 Multiple regression equations for *Rhizoctonia bataticola*

Only 10 out of 16 compounds gave  $ED_{50}$  values less than 1000 mg litre<sup>-1</sup> (Table 2). Thus 10 compounds (**1–9** and **11**) were included and the remaining six compounds ( $ED_{50} > 1000$  mg litre<sup>-1</sup>) were eliminated from this multiple regression study.

##### 1. Best 1-variable model

$$\begin{aligned} pED_{50}(M) &= 0.457\Sigma\sigma - 0.425 \\ n &= 10, R = 0.777, R^2 = 0.605, s = 0.157, \\ F &= 12.229, \text{Prob} > F = 0.0081 \end{aligned} \quad (1)$$

##### 2. Best 2-variable model

$$\begin{aligned} pED_{50}(M) &= 0.474\Sigma\sigma + 0.197\Sigma F - 0.440 \\ n &= 10, R = 0.825, R^2 = 0.680, s = 0.151, \\ F &= 7.430, \text{Prob} > 0.0186 \end{aligned} \quad (2)$$

##### 3. Best 3-variable model

$$\begin{aligned} pED_{50}(M) &= 0.370\Sigma\sigma + 0.413\Sigma F + 0.140\Sigma Es(m) \\ &\quad - 0.337 \\ n &= 10, R = 0.892, R^2 = 0.800, s = 0.130, \\ F &= 7.768, \text{Prob} > F = 0.0173 \end{aligned} \quad (3)$$

##### 4. Best 4-variable model

$$\begin{aligned} pED_{50}(M) &= 0.401\Sigma\sigma + 0.625\Sigma F + 0.321\Sigma Es(m) \\ &\quad + 0.211\Sigma B_4(m) - 0.793 \\ n &= 10, R = 0.962, R^2 = 0.925, s = 0.087, \\ F &= 15.410, \text{Prob} > F = 0.0051 \end{aligned} \quad (4)$$

The electronic parameters,  $\sigma$  and  $F$ , together express 68.0% of the variability of the  $pED_{50}(M)$  value eqn (2). A further introduction of steric parameters like  $Es(m)$  &  $B_4(m)$  successively led to improved correlation ( $R = 0.962$  in eqn (4)). Further addition of other parameters did not produce any significant effect in the correlation. Therefore, eqn (4) is considered to be the best fitted equation for determining fungitoxicity against *R. bataticola*.

#### 3.2.2 Multiple regression equation for *Helminthosporium oryzae*

In the experimental condition, 14 (**1–11** and **14–16**) out of 16 compounds gave  $ED_{50}$  values less than 1000 mg litre<sup>-1</sup> (Table 2) and were thus included for multiple regression study.

##### 1. Best 1-variable model

$$\begin{aligned} pED_{50}(M) &= 4.836 - 0.313\Sigma\pi \\ n &= 14, R = 0.780, R^2 = 0.609, s = 1.092, \\ F &= 18.690, \text{Prob} > F = 0.0001 \end{aligned} \quad (5)$$

##### 2. Best 2-variable model

$$\begin{aligned} pED_{50}(M) &= 4.799 - 0.202\Sigma\pi - 1.123\Sigma\sigma \\ n &= 14, R = 0.883, R^2 = 0.780, s = 0.856, \\ F &= 19.470, \text{Prob} > 0.0002 \end{aligned} \quad (6)$$

##### 3. Best 3-variable model

$$\begin{aligned} pED_{50}(M) &= 4.911 - 0.156\Sigma\pi - 1.100\Sigma\sigma \\ &\quad - 0.099\Sigma L(o) \\ n &= 14, R = 0.904, R^2 = 0.819, s = 0.814, \\ F &= 15.066, \text{Prob} > F = 0.0005 \end{aligned} \quad (7)$$

##### 4. Best 4-variable model

$$\begin{aligned} pED_{50}(M) &= 2.778 - 0.151\Sigma\pi - 1.425\Sigma\sigma \\ &\quad - 0.301\Sigma L(m) + 2.207\Sigma B_4(o) \end{aligned}$$

$$n = 14, R = 0.937, R^2 = 0.878, s = 0.704,$$

$$F = 16.239, \text{Prob} > F = 0.0004 \quad (8)$$

The hydrophobic parameter,  $\pi$  is found to be the variable which best expresses about 60.9% variability of the  $\text{pED}_{50}(\text{M})$  value eqn (5). The variation in the fungicidal activity against *H. oryzae* depends on the change in the physicochemical parameters such as hydrophobic parameter  $\pi$ , electronic parameter  $\sigma$  and steric parameters  $L$  (STERIMOL length parameter) &  $B_4$  (STERIMOL maximum width parameter) for *ortho*-substituents eqn (8). The negative sign associated with  $\pi$ ,  $\sigma$  &  $L(o)$  terms in eqn (8) indicates that the fungicidal activity of the compounds in this series against *H. oryzae* increases with decrease in the values of these parameters, while a positive sign with  $B_4(o)$  indicates that with an increase in the value of  $B_4(o)$ , the fungitoxicity of the phosphonates increases.

Comparison of the two 4-variable models for both the fungi reveals that electronic parameters (viz.  $\sigma$  and  $F$ ) play a significant role in expressing fungitoxicity. Furthermore, the fungicidal activity increases with decrease in hydrophobicity and the electron-withdrawing nature of the benzene ring substituents. Also, the steric parameters are found important in the correlation studies.

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